

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
22 July 2004 (22.07.2004)

PCT

(10) International Publication Number
WO 2004/060269 A3

(51) International Patent Classification⁷: A01N 37/18,
43/04, C12N 15/00, 15/63, C07H 21/04, C07K 1/00

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(21) International Application Number:
PCT/US2003/028512

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(22) International Filing Date:
9 September 2003 (09.09.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT,
RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/436,273 23 December 2002 (23.12.2002) US
60/436,281 23 December 2002 (23.12.2002) US
60/486,533 10 July 2003 (10.07.2003) US
60/486,870 10 July 2003 (10.07.2003) US

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

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(88) Date of publication of the international search report:
14 October 2004

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: MDA-7 AND FREE RADICALS IN THE TREATMENT OF CANCER

(57) Abstract: The present invention relates to methods of treating a cancer in a subject comprising generating within one or more cancer cells of a subject an effective amount of MDA-7 and an effective amount of one or more free radicals. The present invention further relates to methods of inhibiting proliferation or promoting death in a cancer cell of a subject comprising generating within one or more cancer cells of a subject an effective amount of MDA-7 and an effective amount of one or more free radicals. Generation of an effective amount of MDA-7 can occur by administering to the cancer cell an effective amount of an *mda-7* nucleic acid, MDA-7 protein, functional equivalents of either of these molecules, by upregulation of the endogenous *mda-7* gene, or by stabilization of the *mda-7* mRNA. Generation of one or more free radicals in a cancer cell can occur by exposing the cancer cell to an effective amount of ionizing radiation, a free radical, a generator of a free radical, a ROS, a generator of a ROS, or a disruptor of mitochondrial membrane potential.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/28512

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 37/18, 43/04; C12N 15/00, 15/63; C07H 21/04; C07K 1/00

US CL : 514/2, 44; 435/320.1, 455; 536/23.5; 530/350

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 44; 435/320.1, 455; 536/23.5; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, STN, BIOSIS, MEDLINE, CAPLUS, SCISEARCH**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No:
X	WO 01/05437 A2 (INTROGEN THERAPEUTICS, INC.) 25 January 2001 (25.01.2001), pages 11, 12, 134-137.	1-11, 13-19, 24-26, 28-38, 40-46, 51-53, 55-65, 67-73, 78-80
X	WO 02/45737 A2 (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 13 June 2002 (13.06.2002), pages 8, 9, 124-128.	1-9, 20-25, 28-36, 47-52, 55-63, 74-79
Y	SU et al., The Cancer Growth Suppressor Gene Mda-7 Selectively Induces Apoptosis in Human Breast Cancer Cells and Inhibits Tumor Growth in Nude Mice, PNAS, USA, November 1998, Vol. 95, pp. 14400-14405, especially abstract.	1, 10, 11, 13, 15-19, 24, 28, 37, 38, 40, 42-46, 51, 55, 64, 65, 67, 69-73, 78
Y	ADVANI et al., Radiogenetic Therapy: On the Interaction of Viral Therapy and Ionizing Radiation for Improving Local Control of Tumors, Seminars in Oncology, December 1997, Vol. 24, No. 6, pp. 633-638, especially abstract, page 634, left column.	1, 10, 11, 13, 15-19, 24, 28, 37, 38, 40, 42-46, 51, 55, 64, 65, 67, 69-73, 78

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

Special categories of cited documents:	
* "A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

12 August 2004 (12.08.2004)

Date of mailing of the international search report

30 AUG 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/28512

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/28512

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-19, 24-27, 55-73 and 78-81, drawn to a method of treating a cancer or promoting death of a cancer cell in a subject by using a nucleic acid encoding MDA-7 protein.

Group II, claim(s) 1-9, 20-27, 55-63 and 74-81, drawn to a method of treating a cancer or promoting death of a cancer cell in a subject by using a MDA-7 protein.

Group III, claim(s) 28-46 and 51-54, drawn to a method of inhibiting proliferation of a cancer cell in a subject by using a nucleic acid encoding MDA-7 protein.

Group IV, claim(s) 28-36 and 47-54, drawn to a method of inhibiting proliferation of a cancer cell in a subject by using a MDA-7 protein.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the "special technical feature" shared by groups I-IV is the use of nucleic acid encoding MDA-7 protein or MDA-7 protein in combination with free radicals, such as radiation therapy. WO 01/05437 teaches cDNA sequence encoding MDA-7 and expression of MDA-7 protein inhibits growth and induce apoptosis in cancer cell lines (e.g. p. 88). WO 01/05437 also teaches a method of treating a hyperproliferative disease, such as cancer, in a subject by administering an adenoviral expression construct comprising a nucleic acid encoding a human MDA-7 protein under the control of a promoter operable in eukaryotic cells in combination with anti-cancer agents, such as chemotherapy agents and radiotherapy agents (e.g. p. 63-64). Therefore, no "special technical feature" has been contributed by the present invention over the prior art. Thus, groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1.